

# Effect of Topical 0.1% Indomethacin Solution Versus 0.1% Fluorometholon Acetate on Ocular Surface and Pain Control Following Laser Subepithelial Keratomileusis (LASEK)

Federico Badalà, MD,\* Mauro Fioretto, MD,\*†‡ and Angelo Macri, MD§

**Purpose:** To compare the effect of topical 0.1% indomethacin solution versus 0.1% fluorometholon acetate in the early postoperative period after LASEK treatment.

**Methods:** One hundred thirty-five patients undergoing LASEK, having been randomized in a double-masked manner into 2 groups (1 receiving indomethacin and 1 fluorometholon), were evaluated 2–4 days before and 4 days after treatment. We examined corneal fluorescein staining and corneal esthesiometry; the level of pain experienced was reported by the patient on a visual pain scale. In addition, haze was evaluated at  $14 \pm 1$  weeks after surgery.

**Results:** The pain level and corneal fluorescein staining were significantly less in the indomethacin group. Corneal esthesiometry was reduced to the same extent in the 2 groups. There were no statistically significant differences in haze presentation between the 2 groups.

**Conclusion:** Our study highlights the efficacy of indomethacin solution compared with fluorometholon as a pain reducer after LASEK treatment and suggests that indomethacin is associated with a faster epithelial healing process.

**Key Words:** indomethacin, fluorometholon acetate, ocular surface, corneal esthesiometry, LASEK

(*Cornea* 2004;23:550–553)

Laser subepithelial keratomileusis (LASEK) is a relatively new refractive surgical technique that purportedly combines the advantages of laser in-situ keratomileusis (LASIK) and photorefractive keratectomy (PRK). An epithelial flap is created after application of a 15–20% ethanol solution to the cornea to loosen the anchoring structures of the epithelium,

and repositioned after the anterior stromal ablation, so the stromal wound is covered immediately after surgery. According to some authors this results in substantially less pain and faster rehabilitation than PRK. As in PRK, because the procedure is performed on the anterior cornea, there are virtually no flap- or interface-related complications, but it is important that alcohol exposure lasts no more than 30 seconds, as a longer exposure time seems to be related to a significant increase in epithelial cell death.<sup>1–4</sup>

The efficacy of topical indomethacin 0.1% solution and 0.1% fluorometholon acetate after PRK and LASIK has extensively been described.<sup>5,6</sup>

The aim of our study is to compare the effect of indomethacin and fluorometholon on epithelial healing and pain control following LASEK.

## MATERIAL AND METHODS

Between March 2002 and October 2002, 204 consecutive patients undergoing LASEK came under our observation at Microchirurgia Al Eye Clinic (Alessandria, Italy).

Inclusion criteria were:

1. Age between 24 and 40 years
2. Refractive error between –2 and –6.50 D (spherical equivalent)
3. Schirmer 1 test  $\geq 15$  mm
4. Fluorescein clearance test (standardized visual scale  $< 3$ )<sup>7,8</sup>
5. Corneal fluorescein staining score equal to 0
6. Corneal esthesiometry  $\geq 5$  (Cochet Bonnet esthesiometer)

## Schirmer Test

Without previously instilling anesthetic drops, Schirmer paper test strips (Alcon Laboratories, Fort Worth, TX) were placed over the lid margin at the junction of the lateral and middle thirds of the lower eyelid for 5 minutes. The millimeters of strip wetting were measured and recorded.

## Standardized Visual Scale Test (SVST)

Tear fluorescein clearance was evaluated by using the standardized visual scale test.<sup>7,8</sup>

Received for publication July 8, 2004; revision received January 8, 2004; accepted January 13, 2004.

From the \*Departments of Neuroscience, Ophthalmology, and Genetics, University of Genoa, Genoa, Italy; †Ophthalmology Unit, Santo Spirito Hospital, Casale Monferrato, Alessandria, Italy; ‡Microchirurgia Al Eye Clinic, Alessandria, Italy; and §Ophthalmology Unit, San Martino Hospital, Genoa, Italy.

Reprints: Angelo Macri, Via Strasserra 6/18, 16146 Genova, Italy (e-mail: macria@libero.it).

Copyright © 2004 by Lippincott Williams & Wilkins

The standardized visual scale has a score ranging from 0 to 6. The score of 3, corresponding to the fluorophotometric value of 274 fluorescein units/ $\mu\text{L}$ , represents the threshold between normality and abnormality.

Briefly, the color of the tear meniscus in the lateral third of the lower lid was visually compared with one of the colors of the standardized visual scale.

If the color of the tear meniscus was judged to be between 2 of the 6 standard scale colors, then the score was graded between these two standard colors. For example, if the color was stronger than 2 but weaker than 3, it would be graded 2.5.<sup>7,8</sup>

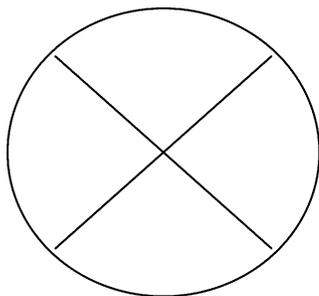
All the patients enrolled in this study should have a SVST score < 3.

### Corneal Fluorescein Staining

The ocular surface was examined with a biomicroscope and the  $\times 10$  objective under blue-light illumination 2 minutes after fluorescein instillation into the tear film. The intensity of corneal fluorescein staining was recorded as previously described<sup>7,8</sup> in each of 4 quadrants on the cornea—temporal, nasal, superior, and inferior—using a standardized 4-point scale (0 = none; 1 = mild; 2 = moderate; 3 = severe). The range of staining scores was from 0 to 12 (Fig. 1).

### Cornea Sensitivity

Cornea sensitivity was assessed with the Cochet-Bonnet esthesiometer (Luneau Ophtalmologie, Chartres Cedex, France).<sup>7,8</sup> The stimulus from the Cochet Bonnet consists of a nylon filament that can be varied in length from 0 to 6 cm. The procedure for measuring ocular surface sensitivity was as follows: under visual control, the nylon filament of the Cochet Bonnet instrument was approached smoothly and perpendicularly toward the center of the cornea. Contact was detected by the slightest bend of the nylon; sensitivity was taken as the length of the filament that gave a 50% positive response from a minimum of 4 stimulus applications. Subject reliability was



**FIGURE 1.** Corneal fluorescein staining. The cornea was schematically divided into 4 sectors, and a score ranging from 0 to 3 was assigned to each sector. The total score for each cornea ranged from 0 to 12.

tested by bringing the filament close to the cornea without actually touching.

Each of these above-mentioned tests was performed 2–4 days before surgery ( $T_0$ ).

Postoperative examination (corneal esthesiometry, corneal fluorescein staining, pain evaluation) was done by masked observers at postoperative day 4 ( $T_1$ ).

Postoperative pain level was assessed by the patient at postoperative day 4 using a “visual pain scale” (VPS) with values ranging from 0 to 10 (0 = no pain; 10 = most severe pain imaginable; Fig. 2). Each patient was asked to summarize the pain experienced from surgery up to the moment of the test.

Furthermore, haze was evaluated at  $14 \pm 1$  weeks ( $T_2$ ) after LASEK following Fantes’ classification.<sup>9</sup>

### SURGERY PROCEDURE

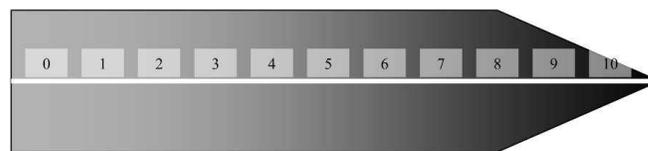
The eye to be operated on received 2 drops of propacaine hydrochloride 0.5%. Preincision of the corneal epithelium was performed with a special microtrephine with a 9.0-mm diameter, 70  $\mu\text{m}$  deep calibrated blade. An alcohol solution cone with a 9-mm diameter was placed on the eye. Then 0.1 mL of a 15% ethanol–sterile water solution was instilled inside the alcohol solution cone and left for 20 seconds. The area was washed with balanced salt solution. A thin abrasion of 0.75 mm was made on the paracentral corneal epithelium, from 8 to 11 o’clock. The epithelium was gently dissected with a Vinciguerra/Carones spatula, and the epithelial flaps obtained were folded nasally and temporally. Photoablation was performed using a Laserscan 2000 (Lasersight, Orlando, FL). This machine uses a galvanometric scanning delivery system (flying spot) with repetition rate 100 Hz, fluence 160  $\text{mJ}/\text{cm}^2$ , and beam diameter 1 mm.

Six-millimeter optical zones and 9-mm transition zones were usually obtained.

After the refractive laser ablation, the epithelial flaps were gently repositioned with the above-mentioned spatula with the margins overlapped.

Finally a protective soft contact lens  $-0.50$  sf refractive power was placed (Acuvue, Johnson & Johnson).

Patients were randomly assigned in a double-masked manner to receive after LASEK a topical treatment of either 0.1% indomethacin solution (Indocollirio, Bausch & Lomb



**FIGURE 2.** Analogue visual pain scale. At  $T_1$  (postoperative day 4) all the subjects enrolled in the study were asked to mark a number on the pain scale shown below representing the average level of pain from LASEK to the moment of the test.

Fidia Oftal, Catania, Italy) with thimerosal 0.5 mg as preservative or 0.1% fluorometholon acetate (Flarex, Alcon, Milano, Italy) with benzalkonium chloride 0.01% as preservative. These drugs were applied 4 times a day for 4 days. The test eye drops (0.1% indomethacin solution and fluorometholon 0.1% acetate) were identical to the commercial drugs available in Italy, except for the removal of all identifying labels and the reconditioning of the drugs in identical individual vials. This resulted in clear, indistinguishable solutions for the 2 treatments. Test drops were identified by the clinical trial registration number and the randomization number only. Topical eye drops for all patients included preservative-free 0.3% netilmicin (Nettacin preservatives free, Sifi, Catania, Italy) and preservative-free 0.2% hyaluronic acid (HY-DROP, Bausch & Lomb Fidia Oftal, Catania, Italy) 4 times a day. In addition, patients were prescribed paracetamol (500 mg)–codeine (30 mg) sachets (Tachidol, Angelini, Roma, Italy) once a day.

The medication for both groups included the use, for 4 days, of soft contact lenses  $-0.50$  sf refractive power (Acuvue, Johnson & Johnson).

For statistical purposes we considered only 1 eye, randomly chosen, for each patient.

With Excel 2002 (Microsoft), random numbers (0–1) were assigned to each patient; 2 groups were obtained in this way.

Data distribution was evaluated. For normally distributed data, parametric tests were used; otherwise nonparametric tests were used (GraphPad Prism 2.0 Software).

## RESULTS

Out of 204 patients, 161 matched inclusion criteria and were enrolled in our study.

During the study 12 patients were excluded because of accidental contact lens removal and another 14 patients because of low compliance with other instructions (not taking medications as prescribed). Patients excluded from the study were equally distributed between the 2 groups.

A total of 135 patients were considered for statistical analysis.

Patient demographics are detailed in Table 1.

Age and degree of preoperative refractive error in the eye that was operated on was not significantly different in the 2 treatment groups (2-tailed *t* test; *P* not significant).

**TABLE 1.** Patient Demographics

	NSAIDs Group	Steroid Group
N	69	66
Age	29.2 ± 3.4	28.7 ± 3.5
Refractive error (D)	-3.1 ± 1.8	-3.0 ± 1.9

Mean ± SD. Refractive errors are expressed as spherical equivalent.

Differences in corneal fluorescein staining (Mann-Whitney  $U = 447$ ;  $P < 0.0001$ ) and pain level (Mann-Whitney  $U = 198$ ;  $P < 0.0001$ ) were statistically significant between the 2 groups (Table 2).

Differences in corneal sensitivity and in corneal haze between the two groups at  $T_0$  and  $T_1$  were not statistically significant (Mann-Whitney  $U$  test; *P* not significant)

## DISCUSSION

LASEK is a relatively new technique to reduce refractive error. According to some authors it causes less postoperative pain and haze and results in a shorter visual recovery time than PRK, though according to others the differences are not significant.<sup>1,10,11</sup>

In the early postoperative time after PRK and LASEK, it is common practice to use steroid and nonsteroidal antiinflammatory drug (NSAID) eye drops either in association or independently.

NSAIDs inhibit cyclooxygenase activity, thereby preventing endoperoxide and prostaglandin formation.<sup>12,13</sup> Prostaglandins are produced in the cornea by the epithelium and the stroma. They are known to increase the sensitivity of pain receptors. Many studies demonstrated the efficacy of topical NSAIDs to reduce corneal pain. In particular, the corneal analgesic action of indomethacin has been extensively described.<sup>14</sup>

The effect of topical steroids for the modulation of postoperative inflammation has been largely investigated, and their role on wound healing and reduction of anterior stromal haze and regression of the refractive effect remains controversial. Some authors demonstrated that corticosteroids have no significant long-term effect on corneal haze or visual outcome after PRK.<sup>15–18</sup> Other studies have demonstrated that steroids

**TABLE 2.** Pain Level, Corneal Fluorescein Staining, and Cochet Bonnet Esthesiometry in the 2 Groups Before ( $T_0$ ) and After ( $T_1$ , postoperative day 4) LASEK

	$T_0$	$T_1$ *
Corneal fl. staining, steroid group	0	4.07 ± 2.75
Corneal fl. staining, NSAIDs group	0	1.42 ± 1.27
Pain level, steroid group	0	6.03 ± 1.48
Pain level, NSAIDs group	0	2.12 ± 2.02
Cochet Bonnet esthesiometry, steroid group	5.97 ± 0.13	4.96 ± 0.85
Cochet Bonnet esthesiometry, NSAIDs group	5.94 ± 0.22	4.54 ± 0.66
Haze in NSAIDs group	0	0.40 ± 0.19
Haze in steroid group	0	0.39 ± 0.21

Mean ± SD. Fl., fluorescein.

\*The time  $T_1$  for haze rows is 14 ± 1 weeks.

were effective in limiting haze and myopic regression after PRK, particularly after higher myopic corrections.<sup>19–22</sup>

Patients enrolled in our study occasionally presented mild haze, and no differences in the 2 treatment groups were observed. This is not surprising considering the low mean refractive error.

NSAIDs and steroid eye drops have been extensively evaluated and compared after PRK, though there is still not much literature following LASEK.

This prospective randomized, double-masked study compares indomethacin 0.1% solution with 0.1% fluorometholon in the early postoperative period following LASEK.

No significant differences in corneal sensitivity and in haze were observed between the 2 groups.

In conclusion, indomethacin is much more effective than fluorometholon in reducing postoperative pain and resulted in earlier epithelial recovery.

## REFERENCES

- Soong HK, Dastjerdi MH. LASEK (laser subepithelial keratomileusis). *Curr Opin Ophthalmol*. 2002;13:261–263.
- Gabler B, Winkler von Mohrenfels C, Dreiss AK, et al. Vitality of epithelial cells after alcohol exposure during laser-assisted subepithelial keratectomy flap preparation. *J Cataract Refract Surg*. 2002;28:1841–1846.
- Feit R, Taneri S, Azar DT, et al. LASEK results. *Ophthalmol Clin North Am*. 2003;16:127–135.
- Chen CC, Chang JH, Lee JB, et al. Human corneal epithelial cell viability and morphology after dilute alcohol exposure. *Invest Ophthalmol Vis Sci*. 2002;43:2593–2602.
- Vetruigno M, Quaranta GM, Maino A, et al. A randomized, comparative study of fluorometholone 0.2% and fluorometholone 0.1% acetate after photorefractive keratectomy. *Eur J Ophthalmol*. 2000;10:39–45.
- Assouline M, Renard G, Arne JL, et al. A prospective randomized trial of topical soluble 0.1% indomethacin versus 0.1% diclofenac versus placebo for the control of pain following excimer laser photorefractive keratectomy. *Ophthalmic Surg Lasers*. 1998;29:365–374.
- Macri A, Pflugfelder SC. Correlation of Schirmer I test and fluorescein clearance tests with the severity of corneal epithelial and eyelid disease. *Arch Ophthalmol*. 2000;118:1632–1638.
- Macri A, Rolando M, Pflugfelder SC. A standardized visual scale for evaluation of tear fluorescein clearance. *Ophthalmology*. 2000;10:1338–1343.
- Fantes FE, Hanna KD, Waring GO 3rd, et al. Wound healing after excimer laser keratomileusis (photorefractive keratectomy) in monkeys. *Arch Ophthalmol*. 1990;108:665–675.
- Vinciguerra P, Camesasca F. Butterfly laser epithelial keratomileusis for myopia. *J Refract Surg*. 2002;18:S371–S373.
- Lee JB, Seong GJ, Lee JH, et al. Comparison of laser epithelial keratomileusis and photorefractive keratectomy for low to moderate myopia. *J Cataract Refract Surg*. 2001;27:565–570.
- Flach AJ. Cyclo-oxygenase inhibitors in ophthalmology. *Surv Ophthalmol*. 1992;36:259–284.
- Phillips AF, Szerenyi K, Campos M, et al. Arachidonic acid metabolites after excimer laser corneal surgery. *Arch Ophthalmol*. 1993;111:1273–1278.
- Patrone G, Sacca SC, Macri A, et al. Evaluation of the analgesic effect of 0.1% indomethacin solution on corneal abrasions. *Ophthalmologica*. 1999;213:350–354.
- Aras C, Ozdamar A, Aktunc R, et al. The effects of topical steroids on refractive outcome and corneal haze, thickness, and curvature after photorefractive keratectomy with a 6.0-mm ablation diameter. *Ophthalmic Surg Lasers*. 1998;29:621.
- Gartry DS, Kerr-Muir MG, Marshall J. The effect of topical corticosteroids on refraction and corneal haze following excimer laser treatment of myopia: An update. A prospective, randomized, double-masked study. *Eye*. 1993;7:584.
- O'Brart DP, Lohmann CP, Klonos G, et al. The effects of topical corticosteroids and plasmin inhibitors on refractive outcome, haze, and visual performance after photorefractive keratectomy. A prospective, randomized, observer-masked study. *Ophthalmology*. 1994;101:1565.
- Corbett MC, O'Brart DP, Marshall J. Do topical corticosteroids have a role following excimer laser photorefractive keratectomy? *J Refract Surg*. 1995;11:380.
- Baek SH, Chang JH, Choi SY, et al. The effect of topical corticosteroids on refractive outcome and corneal haze after photorefractive keratectomy. *J Refract Surg*. 1997;13:644.
- Choi SY, Kim HY, Kim JY, et al. Two-year follow-up of eyes without topical corticosteroid treatment after photorefractive keratectomy (PRK). *Korean J Ophthalmol*. 1998;12:25.
- Vetruigno M, Maino A, Quaranta GM, et al. The effect of early steroid treatment after PRK on clinical and refractive outcomes. *Acta Ophthalmol Scand*. 2001;79:23–27.
- Hersh PS, Rice BA, Baer JC, et al. Topical nonsteroidal agents and corneal wound healing. *Arch Ophthalmol*. 1990;108:577–583.